IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 057491/0413

In re patent application of
MASCARENHAS

Group Art Unit: 1654

Serial No. 09/399,120

Examiner: Anish GUPTA

Filed: September 20, 1999

For: NULL IGF FOR THE TREATMENT OF CANCER

DECLARATION UNDER 37 CFR § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

I, Andreas Sommer, hereby declare that:

1. I am a principal scientist at INSMED, the assignee of the captioned application. I have worked in the field of protein chemisty, growth factor biology, including the study of the insulin-like growth factor family (IGFs), and preclinical and clinical protein drug development. I have published over 40 papers in this field. My qualifications are set out in my *curriculum vitae*, which is attached hereto as APPENDIX A.

2. I have reviewed and understood the subject application and the final office action dated November 5, 2002. As set out in detail below, it is my opinion that, based on the instant specification, one of skill in the art would be able to recognize the therapeutic potential of a null IGF, identify the null IGFs suitable for practicing the methods of the present invention, and establish appropriate protocols for using such null IGF compounds in the treatment of a cancer.

3. It is my understanding that the PTO is contending that none of the null IGF compounds disclosed in the instant invention are enabled for slowing the growth rate or progression of cancer, including prostate cancer. It is also my understanding that, based on the examiner's comments during an interview dated February 26, 2003, the Office doubts the predictive value of therapeutic data in a PC-3 xenograft animal model. In particular, I understand that the Office is of the opinion

that the PC-3 animal model cannot sufficiently mimic human prostate cancer and therefore cannot be used to predict the therapeutic utility of a null IGF.

4. The null IGF technology described in the present invention takes advantage of IGF-I analogs that have lower affinity for an IGF-I receptor than a wild-type IGF, yet bind the major IGF binding protein-3 (IGFBP-3) with equal, nearly equal, or better affinity that the wild-type IGF. In this regard, a [Leu 60] IGF (*i.e.*, Y60L), for example, can be used to slow wild-type IGF-induced cellular growth, including tumor cell growth, and improve the survival rate. This is demonstrated in the PC-3 xenograft model used in the present invention.

5. Moreover, it would be reasonable to expect null IGF analogs, such as [Ala31, Leu60] IGF-I; [Leu24, Leu60] IGF-I; [Leu24, Ala31, Leu60] IGF-I; [Leu24, 59, 60, Ala31] IGF-I; [1-27, Gly4, 38-70] IGF-I; [Ser24] IGF-I; [Leu24, 1-62] IGF-I and [1-29, gly, gly, gly, gly, 42-62] IGF-I, to also have anti-cancer benefits based on the data provided in the instant specification. These analogs meet the criteria of reduced binding to the IGF-I receptor and normal or nearly normal binding to IGFBP-3.

6. Other ideal null IGF analogs can be obtained by conservative amino acid changes at any position in the C and/or D domain in an IGF-I molecule. Indeed, the experimental results based on [Leu60] IGF-I that are presented in the instant application clearly indicate that other null IGF analogs that share the same properties as [Leu60] IGF-I would result in the same beneficial effects.

7. It is my belief that the data from the PC-3 xenograft animal model used in the instant invention will predict the therapeutic utility of the above-specified IGF-I analogs in a human cancer. As the invention clearly identifies the molecular target as wild-type IGF, which activates the IGF-I receptor and promotes cellular growth, the described null IGF technology acts to attenuate the growth effects of circulating natural IGFs. Thus, the ability of null IGF to decrease cell growth is not model dependent.

8. Furthermore, recent literature has been presented which implicates various insulin-like growth factors in a variety of carcinomas, including breast, lung, prostate, colorectal and other

cancers. Therefore, as predicted from studies in the PC-3 animal model, a null IGF applied to any cancer associated with IGF-induced cellular proliferation would have an anti-cancer effect.

8. I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: Andreas Sommer Date: 04/02/2003
Andreas Sommer, Ph.D.